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09/744,654	01/29/2001	Tsvee Lapidot	LAPIDO2	2645

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EXAMINER
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/744,654	Applicant(s) Lapidot
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 29, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above, claim(s) *28-32, 34-47, and 50-52* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-27, 33, 48, and 49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response to the restriction requirement received on 10/29/02 has been entered. Claims 1-52 are pending in the instant application. Applicant's election with traverse of the subject matter of Group I, claims 1-27, 33, and 48-49 is acknowledged. Claims 28-32, 34-47, and 50-52 are hereby withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6. Claims 1-27, 33, and 48-49 are currently under examination. An action on the merits follows.

Election/Restriction

As noted above, applicants have traversed the restriction requirement made in paper no. 5. The traversal is on the ground(s) that all the claims share the same special technical feature. THe applicant does not specifically identify the "special technical feature" but states that the special technical feature is recited in claim 1. Claim 1 recites a cell composition consisting essentially of CXCR4+ stem cells capable of migrating in response to SDF-1. As stated in the original restriction requirement, cells which are CXCR4+ stem cells which migrate in response to SDF-1 are naturally occurring cells found abundantly in peripheral blood. Further, the prior art teaches purified compositions of these cells, see for instance Mohle et al. (1998), Blood, Vol. 91, No. 12,

4523-4530. Thus, the cells themselves cannot be considered a special technical feature. Further, the previous office action provided specific reasons why the groups of inventions identified are not so linked as to form a single general inventive concept under PCT Rule 13.1. In short, the cells of Group V are genetically modified and as such are substantially different in structure and function from unmodified cells of Group I. Likewise the non-human chimeric mammal of group II comprises substantially different structural elements than the cells themselves. Also, the methods of Groups III-IV utilize different reagents and methods steps such that the search for each group is not co-extensive. Thus, for the reasons discussed above, applicant's arguments are not found persuasive. The restriction requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Mohle et al. (1998), Blood, Vol. 91, No. 12, 4523-4530. The applicant claims cell compositions consisting essentially of CXCR4+ stem cells capable of migrating in response to SDF-1 and/or capable of adhering to stromal cells in response to an adhesion-inducing agent. The applicant further claims

said compositions wherein the cells are CD38 low, CD34- /CD38 low, CD34+/CD38low, or CD38+. In regards to claims depending on claim 1 which recite various adhesion-inducing agents, please note that the claims recite "and/or" and thus a cell composition which meets the claim limitations only has to demonstrate one or the other of these activities. In addition, in regards to claim 6 and claims depending on claim 6, please note that the claims as written are cell compositions. In regards to composition claims, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). Thus, any cell composition which meets the structural requirements of claim 6, i.e. a cell composition consisting primarily of CXCR4+ cells with some CXCR4 low cells, will be meet the limitations of these claims.

Mohle et al. teaches purified compositions of cells, including CD34 -cells, CD34+ cells, CD34+/CD38low cells, CD38+ cells, and CD38low cells, which express CXCR4 and migrate in response to SDF-1 (Mohle et al., pages 4525-4527, and Figures 1-3). Mohle et al. further teaches human CXCR4+ cells derived patient's peripheral blood, which can be considered either autologous or allogeneic. Mohle et al. further teaches populations of cells wherein the majority of cells express CXCR4 and a subpopulation is CXCR4-/low (Mohle et al, page 4526, Figure 2). Thus, by teaching all the elements of the claims as written, Mohle et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-27, 33, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,541,103, 7/30/96, hereafter referred to as Kanz et al. in view of Mohle et al. (1998), Blood, Vol. 91, No. 12, 4523-4530. The applicant claims methods of increasing the population of hematopoietic stem cells for use in clinical transplantation comprising up-regulating surface CXCR4 expression and sorting out those CXCR4 stem cells that migrate in response to

SDF-1. The applicant further claims said methods wherein CXCR4 is up-regulated by stimulation with cytokines such as IL-6 and SCF, or stromal cells, or stomal cells and a mixture of SCF and IL-6. The applicant further claims methods of screening for cells suitable for transplantation comprising the stimulation of cells with IL-6 and SCF followed by sorting of the cells for SDF-1 responsiveness by carrying out an in vitro transmigration assay across a mechanical barrier of cells wherein the cells to be sorted are the cells which transmigrate in response to SDF-1. Please note that the intended use of the instant methods for preparing cells "for clinical transplantation" recited in the preamble does not constitute a step in the methods as claimed. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure or composition, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. In re Hirao , 535 F.2d 67, 190 USPQ 15 (CCPA 1976); Kropa v. Robie , 88 USPQ 478, 481 (CCPA 1951).

Kanz et al. teaches the preparation of hematopoietic stem cells useful for transplantation comprising stimulating cells with mixtures of cytokines including SCF-1 and IL-6 (Kanz et al., columns 1 and 7-8). In particular, Kanz et al. teaches that CD34+ cells treated with SCF-1 and IL-6 expand in culture and demonstrate increased colony forming potential which increases their usefulness for transplantation (Kanz et al., columns 3-4). Kanz et al. also teaches the stimulation of peripheral blood progenitor cells derived from cancer patients , and further suggests purifying the expanded peripheral blood progenitor cells from contaminating tumor cells (Kanz et al.,

column 4, lines 19-31). Please note that while Kanz et al. does not specifically teach that the administration of SCF-1 and IL-6 results in increased expression of CXCR4 on the progenitor cells, Kanz et al. does teach the exact method steps recited by the claims for up-regulating surface CXCR4 expression. The MPEP states that, "Where the claimed and prior art products are identical or substantially identical in structure or compositions, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. MPEP 211.01 and In re Best, 195 USPQ 430, 433 (CCPA 1997).

Kanz et al. does not specifically teach the sorting of expanded cells that migrate in response to SDF-1 or which adhere to stromal cells. Mohle et al. supplements Kanz et al. by teaching the sorting of CXCR4+ cells by carrying out an *in vitro* transmigration assay across a mechanical barrier of cells wherein the cells to be sorted are the CXCR4+ cells which transmigrate in response to culture supernatant containing SDF-1 (Mohle et al., page 4524, column 2). Mohle et al. further teaches that the culture supernatant containing SDF-1 is derived from MS-5 bone marrow stromal cells. Based on the fact that the culture supernatant of the MS-5 cells line is capable of stimulating transmigration, it would have been *prima facie* obvious to the skilled artisan to use either the MS-5 culture supernatant or the MS-5 cells themselves which secrete SDF-1 in the transmigration procedure taught by Mohle et al. with a reasonable expectation of success. Mohle et al. further teaches that CXCR4+ hematopoietic progenitor cells which migrate in response to SDF-1 would have enhanced capability to migrate and home to the

bone marrow which would increase their usefulness for transplantation (Mohle et al., pages 4523 and 4528).

Based on the motivation provided by Mohle et al. for sorting CXCR4+ progenitor cells which transmigrate in response to SDF-1 for use in transplantation in order to increase stem cell homing and migration, it would have been *prima facie* obvious to further purify the stem cells produced by Kanz et al. by using the transmigration assay taught by Mohle et al. In view of the successful use of the transmigration assay to isolate CXCR4+ stem cells which migrate in response to SDF-1 by Mohle et al., the skilled artisan would have had a reasonable expectation of success in using this methods to sort stem cells produced by the methods of Kanz et al. that migrate in response to SDF-1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite wherein the cells are autologous, allogeneic, or xenogeneic. Since the claims are composition claims, the terms "autologous, allogeneic, and xenogeneic" lack

context. These terms are used to describe the origin of cells in reference to a second population of cells. Since the claims only a recite a single cell population, the use of these terms is indefinite.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER